ACUTE TOXICITY SUMMARY

XYLENES

(technical xylene (o-, m-, p-), xylol)
(o-xylene, ortho-xylene, 1,2-dimethylbenzene, 2-xylene)
(m-xylene, meta-xylene, 1,3-dimethylbenzene, 3-xylene)
(p-xylene, para-xylene, 1,4-dimethylbenzene, 4-xylene)

CAS Registry Numbers: 1330-20-7 (technical), 95-47-6 (o-), 108-38-3 (m-), 106-42-3 (p-)

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**22,000 μg/m³**
Critical effect(s)	eye irritation in healthy human volunteers
Hazard Index target(s)	Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid
Molecular formula	C_8H_{10}
Molecular weight	106.2
Density	0.881 g/cm^3 (o-); 0.860 (m-); 0.861 (p-) @ 20°C
Boiling point	144.4°C (o-); 139.1°C (m-); 138.4°C (p-)
Melting point	-25°C (o-); -47.87°C (m-); 13.3°C (p-)
Vapor pressure	6.6 (o-); 8.39 (m-); 8.87 (p-) mm Hg at 25°C
Flashpoint	17.2°C (o-); 25°C (m-); 25°C (p-) (closed cup)
Explosive limits	unknown
Solubility	insoluble in water; soluble in ethanol, acetone, ether
Odor threshold	1 ppm (Carpenter *et al.*, 1975)
Metabolites	methylbenzoic acids
Conversion factor	1 ppm = 4.34 mg/m³ @ 25°C

III. Major Uses or Sources

As nonexplosive aromatic hydrocarbons, mixtures of the three (technical xylene) isomers are heavily used in the chemical industry and in the petroleum industry as a solvent and gasoline “antiknock” additives. Of the three isomers, p-xylene is produced in the highest quantities in the U.S. for use in the synthesis of terephthalic acid for polymer fibers such as mylar and dacron (HSDB, 1994). However, m-xylene is the most abundant isomer in the environment (Silverman and Schatz, 1991).

IV. Acute Toxicity to Humans

Despite its structural similarity to benzene, xylene does not influence hematopoiesis. The principal systemic effects of acute xylene exposure are on the central nervous system (CNS) but it is also a respiratory and eye irritant. Nelson *et al*. (1943) exposed 10 healthy human volunteers for periods of 3 to 5 minutes to estimated concentrations of 100 or 200 ppm technical grade xylene. The subjects reported eye, nose, and throat irritation at 200 ppm but not at 100 ppm. A significant area of uncertainty arising from the Nelson *et al*. (1943) study is the use of estimated rather than measured exposure concentrations. Carpenter *et al*. (1975) evaluated eye irritation in 7 human volunteers exposed for 15 minutes to 460, 1,000, 2,000, or 3,000 mg/m^3. One volunteer noted mild throat discomfort at 460 mg/m^3, but not at 2,000 mg/m^3. No subjects reported eye irritation at 460 mg/m^3 (106 ppm). Hastings *et al*. (1984) exposed 50 healthy individuals to 100, 200, or 400 ppm mixed xylenes for 30 minutes to evaluate eye, nose, and throat irritation. The percent of subjects reporting eye irritation was 56 for controls (clean air), 60 at 100 ppm, 70 at 200 ppm, and 90 at 400 ppm. The authors concluded there was no effect on eye irritation at 100 ppm because the incidence of irritation was as low as the control group. The data from Nelson *et al* (1943), Carpenter *et al*. (1975), and Hastings *et al*. (1984) taken together are consistent with a human NOAEL for eye irritation of about 100 ppm for at least a 30-minute exposure.

Exposure of sedentary or exercising subjects to a 10-minute peak concentration of 400 ppm (1,736 mg/m^3) resulted in significantly increased uncontrolled body sway in these subjects. Exposure to 200 ppm (868 mg/m^3) xylene for up to 5 hours did not result in CNS disturbances measured by increased body sway (Laine *et al*., 1993). Riihimaki and Savolainen (1980) reported that a single 5-minute exposure to 400 ppm xylene (isomeric form unknown) resulted in lightheadedness and inebriation similar to alcohol intoxication. Deleterious effects on EEG, reaction time, body balance, and manual dexterity were found in 8 healthy volunteers following exposure to 100 ppm (434 mg/m^3) m-xylene for 6 hours/day for 6 days (Savolainen *et al*., 1980). Exposure of 15 volunteers to 100 ppm technical xylene mixed with 20% ethylbenzene for 70 minutes, including 30 minutes of exercise, resulted in significant impairments in short-term memory and other CNS performance tests (Gamberale *et al*., 1978). Because ethylbenzene may have contributed to the CNS effects, definitive conclusions about the effects of xylene cannot be drawn from this study.

Nine healthy male volunteers were exposed to 200 ppm m-xylene 4 hours a day, with or without exercise for 10 minutes at the beginning of each session (Savolainen *et al*., 1985). There were no changes in reaction times, but average and maximal body sway were decreased in a concentration-dependent manner. Exercise had a sway reducing effect. Male volunteers were exposed to 200 ppm m-xylene vapor for 4 hours a day, either sedentary or with 10 minutes periods of exercise twice a day (Savolainen *et al*., 1984). The body balance of the subjects was impaired in the anteroposterior direction. Nine healthy male students were exposed to 200 ppm m-xylene for 4 hours per day at 6-day intervals over 6 consecutive weeks (Savolainen *et al*., 1982). Body sway tended to decrease with exposure. Only minor electroencephalographic effects were noted on 4 hour exposures to 200 ppm m-xylene exposure, and no other adverse effects were noted (Seppalainen *et al*., 1991).

Five volunteers were exposed to 40 ppm xylene for 7 hours/day, 3 consecutive days/week in an inhalation chamber. There was an 11-day break between each 3-day session (Mergler and Beauvais, 1992). Individual differences in olfactory perception thresholds for toluene were noted, but there was no effect of exposure duration.

Predisposing Conditions for Xylene Toxicity

Medical: Unknown

Chemical: In rats, exposure to 300 ppm (1,302 mg/m³) m-xylene mixed with 600 ppm methyl ethyl ketone (MEK) for 6 hours resulted in synergistic effects on liver enzyme induction and glutathione depletion compared to MEK exposure alone (Liira *et al.*, 1991). Xylene may therefore accelerate the metabolism and clearance of some other xenobiotics. However, in the presence of MEK, xylene metabolism was strongly inhibited; this was accompanied by elevation of xylene concentrations in blood and fat. Thus, exposure to xylene in the presence of other solvents may result in increased toxicity.

V. Acute Toxicity to Animals

Six-hour inhalation LC_{50} values in mice for each xylene isomer are: 4,595, 5,267, and 3,907 ppm (19,942, 22,859, 16,956 mg/m³) for o-, m-, and p- xylene, respectively (Bonnet *et al.*, 1979). A 4-hour LC_{50} for mixed xylenes was estimated as 6,700 ppm (29,078 mg/m³) in rats; and a 2-hour LC_{50} was calculated as 9,500 ppm (41,230 mg/m³) in cats (Carpenter *et al.*, 1975).

An increase in liver weight and cytochrome P450 (P450) content was observed in rats exposed to 1,600 ppm (6,944 mg/m³) p-xylene for 6 hours (Simmons *et al.*, 1991). Rats exposed for 6-hours to 300 ppm (1,302 mg/m³) m-xylene showed increased specific liver P450 enzyme activity and depleted liver glutathione concentrations. These effects were enhanced by simultaneous exposure to 600 ppm MEK (Liira *et al.*, 1991).

Pulmonary effects following exposure to 300 ppm (1,302 mg/m³) p-xylene for 6 hours include microsomal membrane damage and decreased lung P450 enzyme content (Silverman and Schatz, 1991). The destruction of rat lung but not liver P450 enzymes by p-xylene has been described by Patel *et al*. (1978), and has been attributed to the formation of a toxic aldehyde metabolite of p-xylene. Single 6-hr exposures of rats to m-xylene caused inhibition of aryl hydrocarbon hydroxylase and CYP2B1 activities in the lung but not the liver (Foy *et al.*, 1996).

VI. Reproductive or Developmental Toxicity

Exposure of pregnant rats for 6 hours/day on days 4-20 of gestation to 200 ppm (868 mg/m³) technical (mixed) xylene resulted in significantly increased incidence of delayed ossification of the skull in the offspring (Hass and Jakobsen, 1993). The rat pups exposed prenatally to 200 ppm xylene displayed significantly decreased motor performance during adolescence. However, a study using p-xylene showed no significant embryotoxic or developmental effects on the CNS as measured by acoustic startle response in rats following exposure to 7,000 mg/m³ (1,613 ppm) throughout gestation (Rosen *et al*., 1986).

All three isomers of xylene cause maternal toxicity and are fetotoxic but not teratogenic at near lethal concentrations in rats (Hudak and Ungvary, 1978; Ungvary *et al*., 1980). Ungvary and Tatrai (1985) showed that exposure of both rats and mice to technical xylene as well as specific isomers resulted in fetotoxic effects such as fetal weight loss and delayed skeletal ossification. Of the 3 isomers, p-xylene exposure is the most toxic to the fetus, since it results in the least maternal toxicity and the greatest fetotoxicity (Barlow and Sullivan, 1982); m-xylene has been shown to cause the greatest maternal toxicity (Hood and Ottley, 1985).

Persistence of neurobehavioral effects was noted in offspring of female rats (Mol:WIST) exposed to 500 ppm technical xylene for 6 hours per day on days 7-20 of prenatal development. The dose was not maternally toxic and did not decrease viability of offspring. Learning and memory abilities with spatial navigation on a water maze were impaired at 16, 28 and 55 weeks of age. However, differences were not significant at 55 weeks. The authors suggested these results were compatible with two different conclusions: 1) the effect was partly reversible over a long time period, or 2) practice at solving the problem led to compensation over unresolved neurotoxic effects (Hass *et al*., 1997). Rats of the same strain (Mol: WIST) exposed prenatally to the same regimen did not show any differences from control rats in synaptosomal cytosolic calcium concentration (Edelfors *et al*., 1996).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 22,000 μg/m³

Study	Hastings *et al*., 1984 (with support from Carpenter et al., 1975; Nelson *et al*., 1943)
Study population	50 healthy human volunteers
Exposure method	30 minute exposures to 430, 860 or 1720 mg/m³ xylene (technical grade)
Critical effects	subjective reports of eye, nose, and throat irritation
LOAEL	860 mg/m³
NOAEL	430 mg/m³ (100 ppm)
Exposure duration	30 minutes
Equivalent 1 hour concentration	50 ppm (C^1 * 60 min = 100 ppm * 30 min)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	5 ppm (22 mg/m³, 22,000 μg/m³)

With the possible exception of inconsistently observed developmental endpoints, irritation is the lowest reported human health effect for xylene.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

The NAS Committee on Toxicology (NRC, 1984) reviewed the toxicological literature for xylene and determined that the CNS was the main target for xylene toxicity. The Committee concluded that the CNS disturbances in humans (Ogata *et al*., 1970; Gamberale *et al*., 1978) were reversible and were similar to those produced by alkyl benzenes and other related compounds. Irritation of the eyes and mucous membranes (Carpenter *et al*., 1975; Nelson *et al*., 1943) was considered, but the purpose of the EEGL is to protect against CNS toxicity in military personnel . Based on these findings, the Committee recommended a NAS-EEGL of 200 ppm (870 mg/m^3). However, it is not clear that an adequate margin of safety is incorporated into this EEGL for use for the general public.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

The IDLH is 900 ppm, based on animal LC_{50} and LC_{lo} estimates divided by a 10-fold uncertainty factor (NIOSH, 1995). The data cited include several 4 hour studies: (1) an 8,000 ppm m-xylene LC_{lo} for rats (Smyth *et al*., 1962); (2) a 4,550 ppm rat LC_{50} for p-xylene (Harper *et al*. 1977); and (3) a 5,000 ppm rat LC50 for xylenes (NPIRI, 1974). The IDLH appears to be based on the Harper *et al*. (1977) data with an extrapolated 30-minute LC_{50} estimate of 9,100 ppm.

VIII. References

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